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FENTANYL SYNTHETIC METHODOLOGY: A COMPARATIVE STUDY

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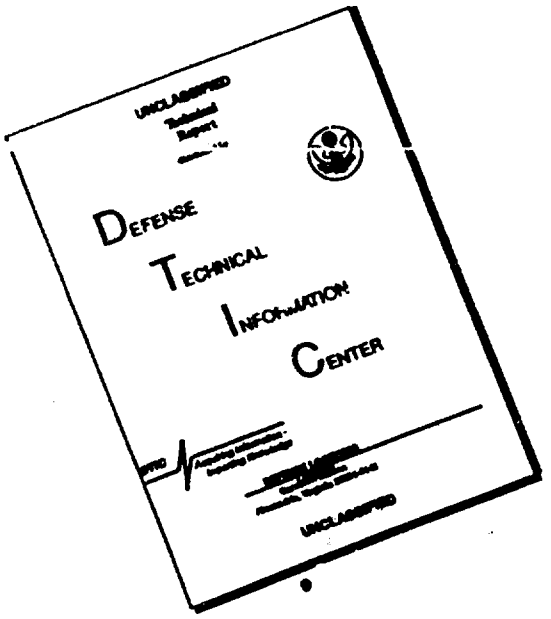

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A literature review has identified six promising methods for the synthesis of fentanyl. Those methods have been compared for overall efficiency. The best method to date is identified.

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PREFACE

The work described in this report was authorized under Project No. 1C161102A71A, Research in CW/CB Defense. This work was started in September 1988 and completed in December 1991.

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FENTANYL SYNTHETIC METHODOLOGY: A COMPARATIVE STUDY

1. INTRODUCTION

The introduction of fentanyl in the 1960's by Janssen Pharmaceuticals was a momentous milestone in man's search for the ideal analgesic; i.e., a drug that provides relief from the excruciating pain of deep wounds or burns without unacceptable side effects. This search has been an endeavor of man from time immemorial. It has been known for at least five thousand years that the dried juice from the unripe seed pod of the opium poppy (*papaver somniferum*) is an extremely effective analgesic. Over the centuries, it was discovered that by carefully drying the juice from the unripe seed pod a useful preparation was produced that could be chewed directly or added to food. However, due to variation in potency depending on growing conditions, harvesting techniques and extraction procedures, the use of this natural product as a medicine in the modern sense of the term did not begin until the most active component was extracted by the German pharmacist, Serturner, in the first years of the nineteenth century[1]. He named this pure compound morphine for its dream-producing properties. It should be noted that the French scientist, Derosne, came extremely close to isolating this compound even earlier[2], and that the experiments of these workers took place more than two decades before the birth of organic chemistry with Wohler's synthesis of urea in 1828.

Morphine was the first alkaloid to be isolated; alkaloids are nitrogen-containing bases derived from plants that often have profound physiological effects. Due to morphine's importance, vigorous attempts were made to elucidate its structure so that it or an even more effective drug could be prepared (hopefully inexpensively) in the laboratory. It soon became clear that unraveling the structure of morphine would be no simple task. Its molecular formula was determined to be $C_{17}H_{19}NO_3$, making for thousands of possible structures.

Before the days of modern spectroscopic techniques, structural assignments were made largely on the basis of degradation. Important structural features of morphine emerged, as did the relationships between morphine and other alkaloids such as thebaine and codeine. After an arduous struggle, spanning more than one century following its isolation, the

correct structure of morphine was deduced by Gulland and Robinson in 1923[3]. By the 1950's this structure was confirmed by total synthesis[4] and X-ray crystallography. Morphine is agonizingly complex, with five rings and five centers of chirality. There are a total of sixteen possible stereoisomers. (Five chiral centers gives rise to a maximum of 2^5 stereoisomers; however, sixteen of these have impossible ring juctions.) In devising an efficient synthesis, even if structural and regioisomerism are successfully addressed, synthetic methodology providing the correct diastereo- and enantioselectivity must be employed. In spite of this formidable challenge, Kenner Rice at the NIH accomplished a total synthesis of the active enantioner of morphine from commercially available 3-methoxyphenethylamine in 20 - 25% yield[5].

While the structure of morphine was being elucidated, a significant discovery was made that resulted in the introduction of first synthetic opioid (not prepared from morphine). Meperidine, a 4-phenylpiperidine, appeared on the market in 1939.[6] It would be satisfying to report that it was prepared after an ingenious intuition concerning those structural features of morphine that produce analgesic activity. In point of fact, it was synthesized as a possible antispasmodic, having an atropine-like structure. Its analgesic activity was discovered later, by accident. Once again serendipity propels science in the right direction. Once again the value of basic, as opposed to goal-directed research, is apparent.

Meperidine, 4-phenyl-4-ethoxycarbonyl-1-methylpiperidine is much simpler structurally than morphine. Prepared in reasonably good yield starting from nitrogen mustard, it has about 60% of morphine's analgesic potency in animal studies. The reversed ester of meperidine, i.e., the propionate ester of 4-phenyl-4-hydroxyl-1-methylpiperidine, was found to have about twice the potency of morphine in pharmacological tests with animals. This discovery spurred further modification of the 4-phenylpiperidine structure, culminating in the 1960's with the discovery of fentanyl, described as a "chemical congener" of the reversed ester.[7] This appears to be a rather broad use of the term congener: Conversion of the 4-position of the reversed ester into that of fentanyl requires replacement of oxygen by nitrogen, followed by transposition of the phenyl group from C_4 to nitrogen. In any event, fentanyl, 4-[1-(2-phenylethyl)piperidinyl]-propanamide, is an extremely potent analgesic, having a potency of about 300 times that of morphine in animal tests. Although it is not the "ideal analgesic," retaining many of the side effects that compromise the use of morphine, it does have significantly lower cardiac depressive effects, and has found extensive use in cardiac surgical procedures.

With the recent expiration of the patent on fentanyl, the following timely report schematically presents six useful routes for the synthesis of fentanyl.

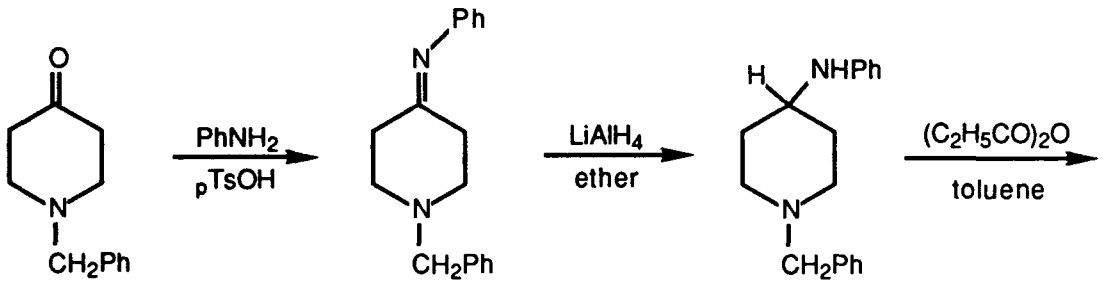
Where appropriate, starting material costs, reaction yields and comments concerning advantages and disadvantages of particular approaches are offered to guide the reader in his selection of the appropriate synthesis or to catalyze new syntheses.

2. SYNTHETIC METHODS

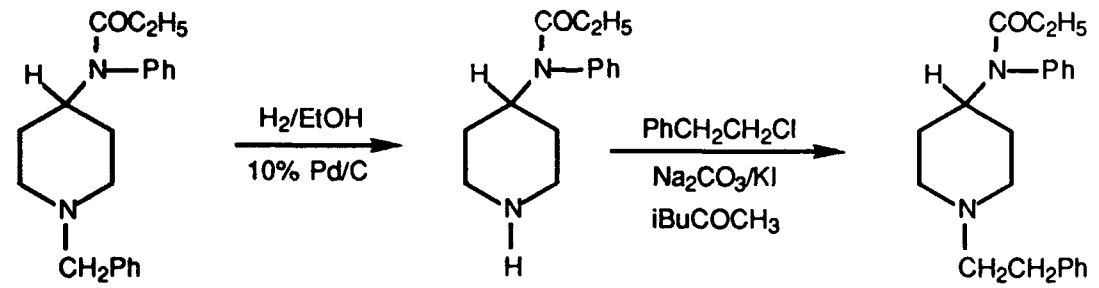
Method A. [8-10]

Fentanyl (1), one of the most potent synthetic narcotic analgesic, was first synthesized in 1964 by Janssen and coworkers. Scheme 1 describes their synthetic route.

Scheme 1



2 **3** **4**



5 **6** **1 Fentanyl**

Condensation of commercially available 1-benzyl-4-piperidone (**2**) (100 g/$53.50, Aldrich) and aniline in the presence of acid catalyst followed by *in situ* lithium aluminum hydride ($LiAlH_4$) reduction of the intermediate Schiff base, **3**, in ether gave compound **4**. Subsequent acylation with propionyl anhydride in toluene followed by hydrogenolysis and alkylation provided the target molecule, **fentanyl** (**1**). However, no yields were given in the patent literature.

Comments:

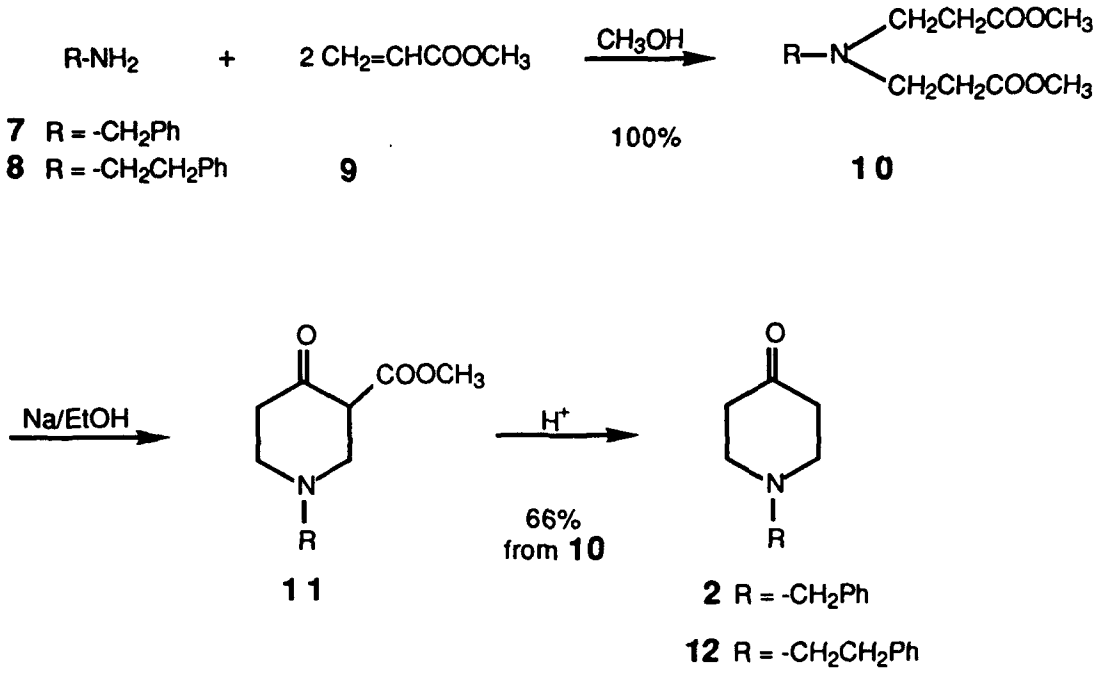
1. Although 1-benzyl-4-piperidone is cheaper, the benzyl group is used as the protecting group, thus, the deprotection and alkylation are required to complete the synthesis, necessarily decreasing yield and convenience.
2. The reducing agent $LiAlH_4$ and the catalyst (10% Pd/C) used in the hydrogenolysis are relatively expensive.
3. The yield of the final alkylation step in carfentanil is low, thus, the same reaction used in fentanyl synthesis may be poor.

Since then many modifications for the synthesis of fentanyl have been reported. These modifications involve the use of either 2-phenethyl analog of **2** as the starting material, or different types of reducing agents.

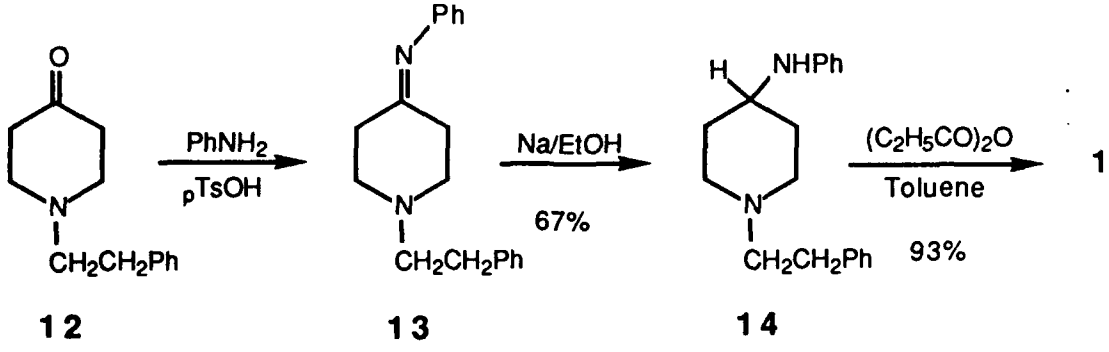
Method B.[11,12]

Zee and his coworkers did systematic studies on each step of the synthesis in order to optimize the yield and to cut down the cost. The starting material, **12** (25 g,/$87.10. Aldrich) can be prepared from phenethylamine (**8**), and methyl acrylate (**9**) in methanol via the intermediate diester, **10**. The hydrolysis yielded the desired 4-piperidone, **12** in good yield (Scheme 2). Reductive amination of ketone **12** and aniline using Na/EtOH as the reducing agent gave **14** in 67% yield. Acylation with propionyl anhydride in toluene gave 93% of fentanyl (Scheme 3).

Scheme 2



Scheme 3



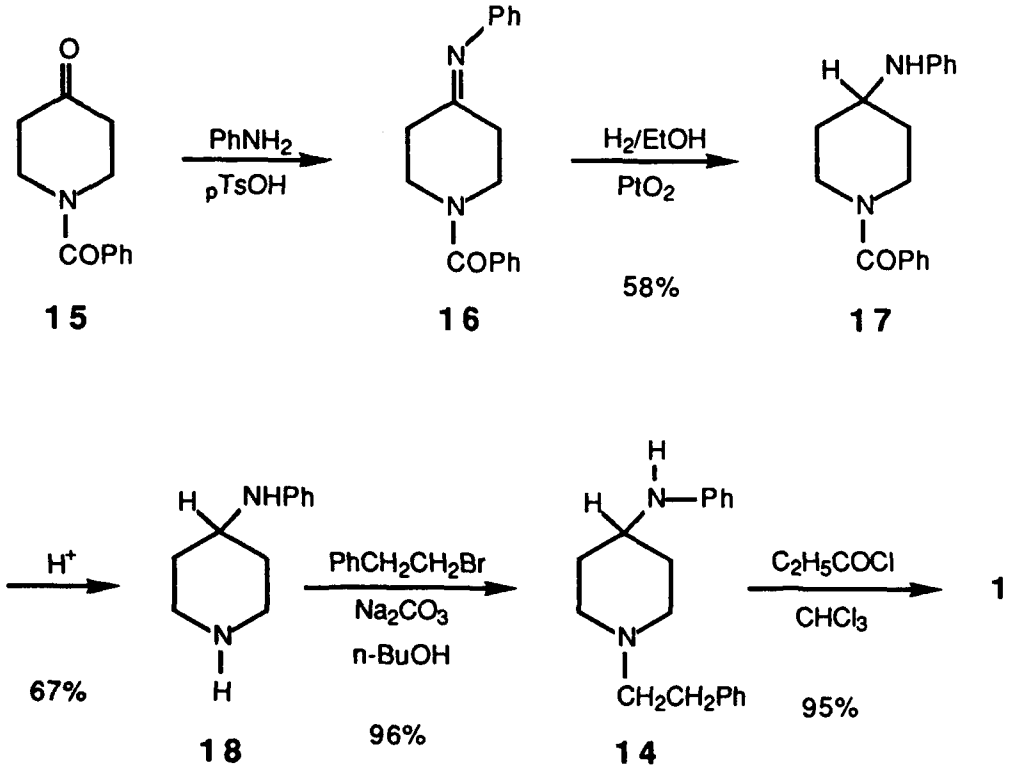
Method C.[13,14]

The reaction sequence is similar to **Method B** except that the $LiAlH_4$ reduction of the Schiff base, **13** gave a 65% of the product.

Method D.[15]

This method utilizes the commercially available 1-benzoyl-4-piperidone (**15**) (1 g/$15.00, Aldrich) as the starting material and the catalytic hydrogenation to reduce the Schiff base, **16**. Acid hydrolysis of **17**, followed by alkylation, gives fentanyl.

Scheme 4

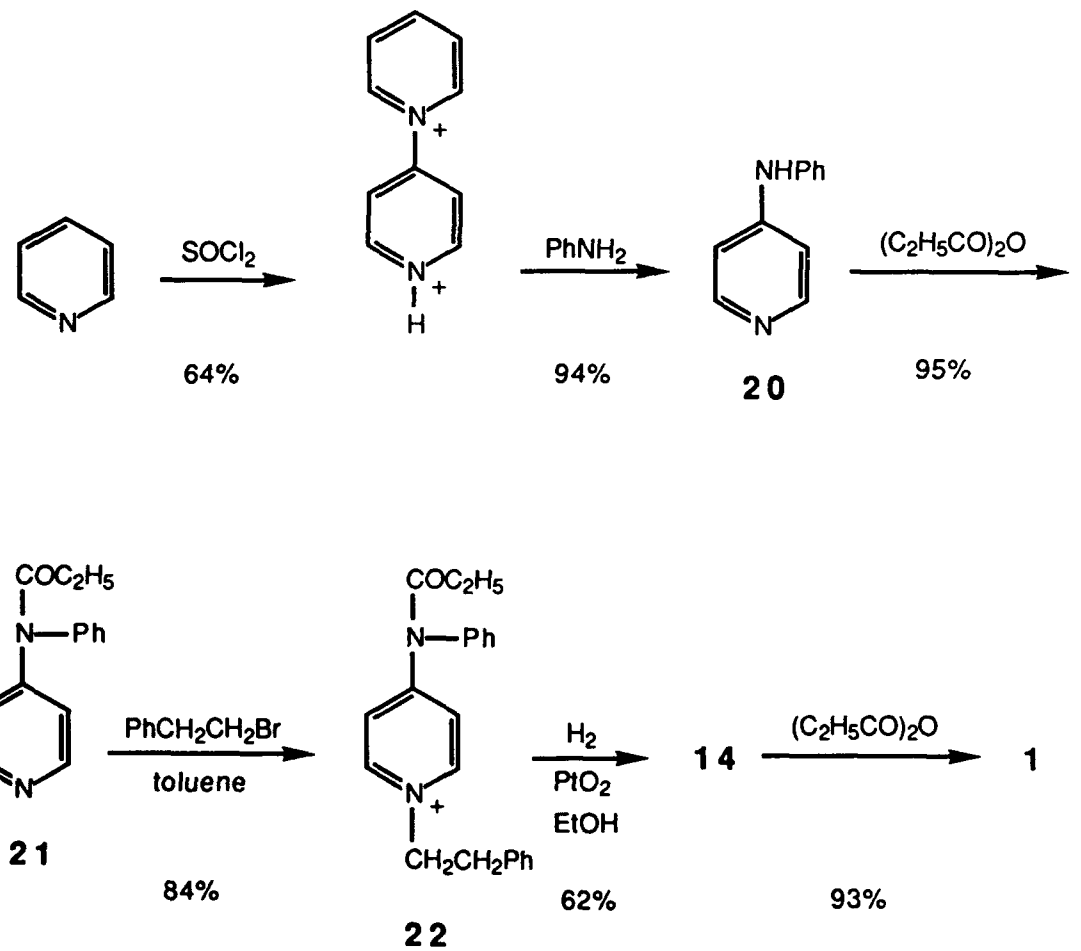


Two additional routes to fentanyl are shown in ***Method E*** and ***F***.

Method E.[16]

The major difference between this method and the others is that the piperidine nucleus of fentanyl is derived from pyridine. Thus, 4-anilinopyridine (**20**) was prepared from pyridine and thionyl chloride. Treatment of **20** with propionic anhydride affords the amide **21**. Subsequent alkylation with 2-phenethyl bromide yields the pyridinium bromide intermediate, **22**. Hydrogenation of **22** over platinum oxide reduces the pyridine ring and also cleaves the propionyl group, affording **14** which can be converted into **1** according to Scheme 4.

Scheme 5

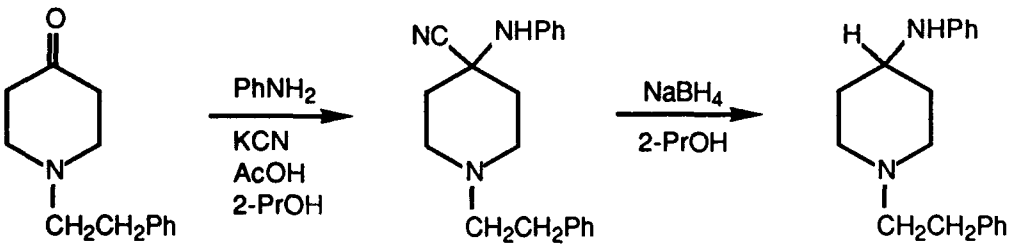


Method F.[17]

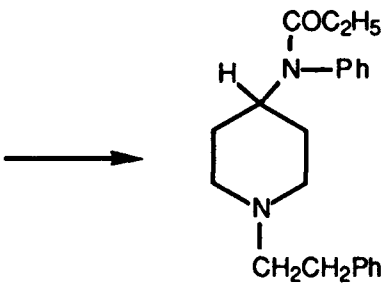
The best yield for the synthesis of **14** is 67% as reported by Zee *et al.* (cf. ***Method B***). An alternate method to prepare **14** has been developed at CRDEC.

The Strecker synthesis of **12** with aniline, KCN, and AcOH in 2-propanol gave excellent yield of α-aminonitrile, **19**. Reductive decyanation of **19** with $NaBH_4$ in 2-PrOH afforded **14** in 85-90% yield. These two steps can be carried out in one pot without the isolation of **19**. Thus, this process represents a considerable improvement over the others.

Scheme 6



12 **19** **14**



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3. CONCLUSION

Scheme 3 represents one of the best procedures for the synthesis of **fentanyl**. Our modification of Scheme 3 has been demonstrated to give the best yield of the product. So this method as shown in Scheme 6 will be further explored at CRDEC.

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